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CURRENT TOPIC

The Use of Adipose-Derived Stem Cells in Cell Assisted Lipotransfer as Potential Regenerative Therapy in Breast Reconstruction

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Abstract

Breast reconstruction for breast cancer patients is performed as a standard of care to improve patients' quality of life, physical and psychosocial well-being. Stem cell therapy holds a promise in regenerative medicine, including in breast reconstruction. This review explores the potential use of adipose-derived stem cells (ADSCs) in cell assisted lipotransfer (CAL) for reconstruction of the breast. The review of literature was done using electronic databases using appropriate keywords, including "adipose-derived stem cell", "stem cell therapy", "adipose-derived stem cell", "cell-assisted lipotransfer", "regenerative therapy", "breast cancer" and "breast reconstruction", with literatures limited to ten years post publication. Adipose-derived stem cells are multipotent cells with angiogenic and immunomodulatory potential. Several studies reveal ADSCs use in CAL results in long-term breast volume retention suggesting improved fat graft survival. Some conflicting outcomes are also discussed, potentially related to numbers of cells enriched and factors affecting the cells' microenvironment. The use of ADSCs in CAL may be beneficial for therapy of breast reconstruction in breast cancer patients after surgical management. Further investigation would be needed to improve the confidence of its clinical use.

Key words: Adipose-derived stem cell; Breast reconstruction; Breast surgery; Regenerative therapy; Cell assisted lipotransfer; Fat graft; Stem cell therapy.

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Introduction

At present, breast cancer still accounts as the most common cancer cases in the female population. According to the World Health Organization, incidence of breast cancer vary worldwide, in Eastern Africa the incidence is 19.3 per 100,000 women, whilst in Western Europe incidence reaches 89.7 per 100,000 women.[1] In Indonesia, breast cancer accounts for approximately 30.5 % of all cancers diagnosed.[2] Patients with breast cancer are undoubtedly faced with high rate of morbidity and mortality, contributing to a great burden. Patients who died of breast cancer in the year 2018 reached up to 627,000 patients worldwide,[3] whilst in Indonesia it accounted for 21.5 % of deaths in females diagnosed with cancer.[2]

For a majority of patients, surgical management has been widely conducted as a definitive treatment and for some in conjunction with radiation therapy and chemotherapy. Surgeons have used variations of surgical procedures to excise lesion according to different staging of the malignancy, namely breast-conserving surgery such as lumpectomy, partial and segmental mastectomy;

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simple mastectomy, skin-sparing mastectomy, radical/total mastectomy and modified radical mastectomy.

Following surgical excision of lesion, breast reconstruction is commonly opted, performed either immediately after mastectomy or delayed. Reconstruction is desired with the aim to restore cosmesis and structure as much as possible. Considering the morbidity and disfigurement following surgical management, the options of breast reconstruction has been available to all patients as a standard of care. Studies have shown how reconstruction surgery greatly affects the patient's quality of life, physical and psychosocial well-being, amongst others.[4-6]

Stem cell therapy has since dominated the promises in relation to regenerative medicine, including in efforts of reconstructing the breast following breast cancer. Particularly, the potential use of adipose-derived stem cells for this purpose is an exciting focus. Adipose-derived stem cells (ASCs) were first isolated by plastic surgeons, derived from processed lipoaspirate tissue.[7] These cells are identified as multipotent stem cells with the natural capability to differentiate into endodermal, mesodermal and ectodermal cells. To name a few are adipocyte, endothelium, chondrocyte, osteocyte, keratinocyte, hepatocyte, beta islet cell and even neuronal and glial cells.[8-12] Adipocyte derived stem cells are readily available and therefore have been explored in many aspects in regenerative medicine, including in management of wound ischaemia in diabetic patients, bone regeneration, promoting neurogenesis, cardiomyocyte proliferation in heart diseases, among others.[13-16] Understandably, its regenerative properties have made ASCs as a potential novel treatment for application in the complexity of breast reconstruction. This review aims to explore the characteristics of ASCs and its potential in improving reconstruction of the breast following surgical management of breast cancer.

This review of literature was conducted by using electronic databases, namely Pubmed and Ovid. Search terms used were: "stem cell therapy", "adipose-derived stem cell", "adipose-derived stem cell", "cell-assisted lipotransfer", "regenerative therapy", "breast cancer" and "breast reconstruction". In order to emphasise on findings from current research and practices, search results were limited to literatures published after the year 2010.

Results

Stem Cells

Stem cells are cells that have the capability of renewing themselves as well as differentiating into other cell lineages in the body.[8] For this reason, stem cells have been an ever-growing interest in its role in tissue engineering for regenerative therapy purposes. Generally, there are two types of stem cells, embryonic stem cells and adult stem cells. Embryonic stem cells come from embryonic tissue, particularly from the inner cell mass of a blastocyst and have pluripotent characteristic.[17] It means that they are able to form cells or tissues derived from all three germ layers. Whilst adult stem cells have multipotent or unipotent characteristic, which have more limitation in its differentiation, commonly in one germ layer only. Adult stem cells are located in many parts of the body, examples of them are mesenchymal stem cells, haematopoietic stem cells, epidermal stem cells, cardiac stem cells, neural stem cells and many others, which will rise to adult somatic cells.[18] Above all, there are also totipotent stem cells, which can differentiate into cells from all three germ layers as well as extra-embryonic tissues such as the placenta, hence it has the highest potential for differentiation.[17] A zygote is considered as a totipotent cell.

It is possible to create pluripotent cells from adult stem cells or even adult somatic cells to create induced pluripotent stem cells (iPSCs), by way of nuclear transfer or reprogramming.[19] Unfortunately, the therapeutic application of iPSCs have been limited due to ethical issues. Furthermore, conversion of differentiated somatic cells into other types of differentiated cells have been proven to be possible using complex molecular mechanisms involving various transcription factors, a process termed trans differentiation. Such techniques of induced pluripotency or trans differentiation to achieve desired cells have been studied in an array of disorders, such as in neurodegenerative diseases (Parkinson's disease), ischaemic heart disease and vascular diseases, in the hope to create personalised cell therapy for patients.[20-22]

Stem cells have certain specific characteristics according to its type and its lineage. Biomarkers help in identifying different types of stem cells. Markers of pluripotency in human embryonic stem cells namely are Nanog, Sox2 and Oct-4.[23]

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These are transcription factors that govern the functions of such cells in preserving their quiescence. Additionally, cell surface markers have also been used to identify embryonic stem cells, such as SSEA-1, SSEA-4, TRA-1-81 and TRA-1-60.[24] Markers for adult stem cells for example are as follows, haematopoietic stem cells: CD34, CD48, CD150, Sca-1; keratinocyte stem cells: K15, Sox9, CD34; neural stem cells: LeX, CD133, Nestin, EGFR, Sox2, Musashi; intestinal stem cells: Lgr5, Bmi1, muscle stem cells: Pax7, CD34, emerin (EMD), LMNA, VCAM1; adipocyte stem cells: CD90, CD13, CD29, CD44, CD105, CD34, CD73, CD10, CD166, CD59, CD49e, HLA-ABC and STRO-1.[25-29]

Functions of stem cells are greatly affected by the niche in which they reside. Stem cell niche are specialised microenvironment that controls stem cell regulation through cell signalling by way of autocrine, paracrine and systemic pathways, as well as through interaction with extracellular matrix components and other signalling.[30, 31] It may represent substantial starting point in the therapeutic modulation of stem cell activity. Thus, it is important to understand how different niches would control the behaviour of stem cells used in therapeutic purposes.

Adipose-derived stem cells

Adipose-derived stem cells (ADSCs) are essentially mesenchymal stem cells. Mesenchymal stem cells are adult stem cells that were first found in the bone marrow, however have been found in other tissues in the body including in adipose tissue, as well. Other sources of mesenchymal stem cells are in the skin, peripheral blood, skeletal muscle, cartilage, pancreas, heart, lung, dental pulp, cord blood, trabecular bone and periosteum.[32, 33] Adipose tissue is a great source of these cells for therapeutic intentions due to its ease in harvest, in larger quantities, whilst leaving less morbidity in the donor site.

The adipose tissue consists of mature adipocytes that form lobes and stromal vascular fraction (SVF). The exact location of ADSCs in adipose tissue has been unclear, however some sources have speculated it to be concentrated in the vasculature or perivascular area.[34] Adipose-derived stem cells can be retrieved, in the SVF portion of adipose tissue using cellular isolation techniques, alongside other cellular components such as endothelial progenitor cells, keratinocytes, macrophages, lymphocyte and smooth muscle cells.[35]

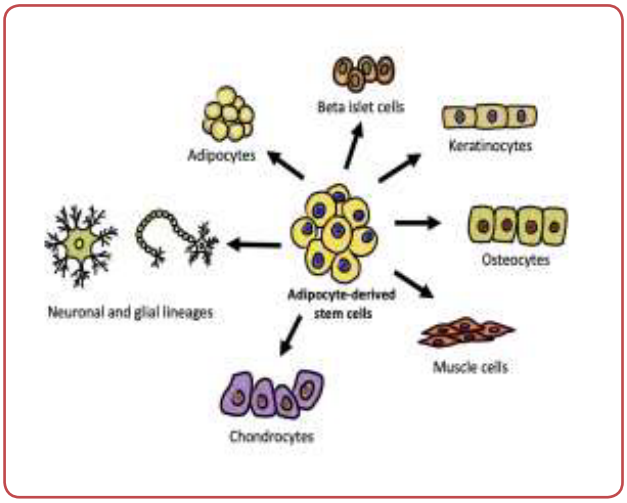

Figure 1: Adipocyte derived stem cell - mesenchymal stem cell with the ability to differentiate into several other cells from all three germ layers

Biomarkers for ADSCs namely are CD90, CD13, CD29, CD44, CD105, CD34, CD73, CD10, CD166, CD59, CD49e, HLA-ABC and STRO-1.[25] They should also be absent of markers such as CD34, CD14, CD11b, CD79a, CD19, CD45, as well as HLA-DR.[8]

Both *in vivo* and *in-vitro,* ADSCs have been proven to be able to differentiate into cells originating from all three germ layers, such as adipocyte, endothelium, osteocyte, chondrocyte, keratinocyte, hepatocyte, beta islet cell, neuronal and glial cells. In itself, ADSCs are essential mesodermal in origin.[8-12] *In vitro* procedure guidelines to induce differentiation of ADSCs into various cell lineages have been studied extensively, using specific induction factors and culture conditions.[10, 36, 37] To illustrate, induction of adipogenic differentiation from ADSCs has been explained by Naderi et al,[38] essentially by cultivating the cells in Dulbecco's Modified Eagle's Medium (DMEM) with 10 % foetal bovine serum (FBS) solution, dexamethasone, insulin, hydrocortisone, indomethacin and 3-isobtyl-1-methylxanthine. Followed by formation of microtissue in hanging drops, its differentiation process assessed using light microscope and lipid staining using Oil Red O, which should show development of lipid droplets in the mature adipocyte. As previously mentioned, stem cells reside in specific niches that regulates the activity and behaviour of these cells. Niche of ADSC is said to be in the perivascular region of adipose tissue, as well as on adventitial vasculogenic zone in blood vessel wall.[39] The niche of ADSCs work similarly to preserve its stemness and clonogenicity, regulating proliferation and differentiation as needed by the tissue by way of interaction

between cells, ECM, growth factors, transcription factors, cytokines and other cell signalling pathways. Jiang et al explained the role of peroxisome proliferator-activated receptor gamma (PPARg) in ADSCs, it leads to activation of platelet-derived growth factor receptor beta (PDGFRß) and vascular endothelial growth factor (VEGFR), which subsequently results in vascular development and stem cell affinity towards the vessel niche.[40] Furthermore, it has been suggested that adenosine receptors has a role in regulating cellular differentiation towards adipogenesis.[41] Changes in glycosaminoglycans expression such as heparan sulphates in ECM and cell surfaces have also shown to affect stem cells' fate from self-renewal to differentiation, through processes that involve protein ligands interactions.[42, 43]

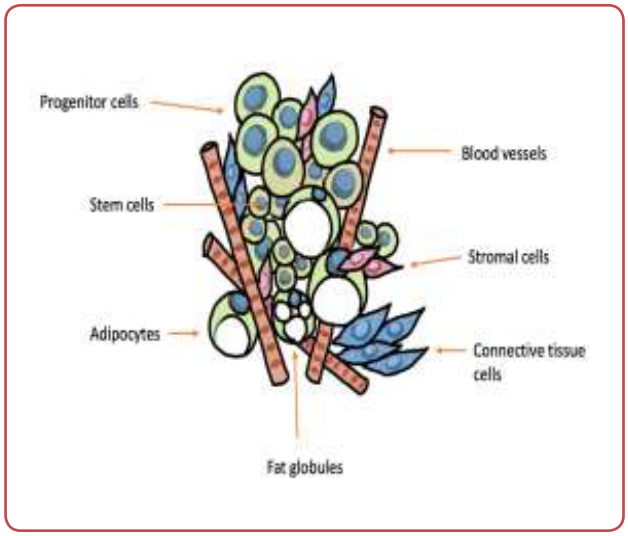

Figure 2: Adipose-derived stem cell niche

The role of ADSCs in relation to wound healing has been studied exponentially. This is generally due to its ability to differentiate into keratinocyte, endothelial cells and fibroblasts, as well as producing cytokines which aids in wound healing.[32] Differentiation into keratinocyte has been observed *in vivo* and *in-vitro*. Culture of ADSCs in collagen matrix along with keratinocyte conditioned media and co-cultured with primary keratinocyte shows differentiation of ADSCs into cobblestone-like structure, suggesting keratinocyte-like cell differentiation.[44] Ebrarhimian et al[45] demonstrated how GFP-positive ADSCs injected in the wound tissue of mice eventually show expression of keratinocyte markers, namely K5 and K14. Fibroblast, a vital component of tissue remodelling in wound healing, was generated from human ADSCs and have shown to produce robust ECM containing collagen 1, fibronectin and elastin *in vitro*.[46] The use of such fibroblast differentiation was used in canine vocal fold injury demonstrating secretion of elastin, hyaluronic acid, decorin, fibronectin and collagen as ECM properties, which is beneficial in wound healing.[47] Finally, vascularisation is important in tissue regeneration and wound healing. Endothelial cell differentiations from ADSCs increase neovascularisation by way of angiogenesis in ischaemic tissue. Some angiogenic factors secreted by endothelial cells from ADSCs include VEGF and hepatocyte growth factor (HGF) which are essential in vasculogenesis.[48]

The ability of ADSCs to secret an array of cytokines, chemokines and growth factors play an important role in tissue healing and regeneration. These substances essentially help in many stages of wound healing, from induction of cell proliferation and migration, promoting angiogenesis and generation of epithelial cells, as well as remodelling. Besides VEGF and HGF, ADSCs are able to secrete angiogenic cytokines such as PDGF, GM-CSF, bFGF, SDF-1, TGF-ß, IL-8, IL-6, FGF2 and MMP.[48, 49] Additionally, ADSCs also produce cytokine that regulates proliferation and migration of fibroblasts, such as VEGF, bFGF, EGF and PDGF-AA.[50]

Cell Assisted Lipotransfer in Breast Reconstruction

Isolation of ADSCs is done by initially performing liposuction or direct excision of fat tissue in the trunk area or extremities such as the thigh and buttocks (Coleman technique), followed by isolation of cells from the stromal vascular fraction using enzymatic processes and cellular centrifugation.[51] Lipotransfer using autologous fat graft is then conducted using fat tissue that has been enriched with the isolated ADSCs or SVF. The high regenerative and proliferative potential of these cells are expected to support the graft survival against fat absorption and encourage wound healing.[52] Several types of cell-assisted lipotransfer (CAL) techniques are commercially available to be used by plastic surgeons.

Mesenchymal stem cell from adipose tissue has shown yield of number of stem cells that is higher than in the bone marrow per gram of tissue.[53] The clonogenic ability of ADSCs, as well as potential to differentiate into adipocytes, endothelial and epithelial cells warrants its therapeutic use in regenerating the breast structure. The angiogenic properties is expected to enhance regeneration of

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blood vessel in the fat tissue, potentially improve graft survival and reduce postoperative absorption.[54]

Domenis et al demonstrated *in vitro* differentiation of isolated ADSCs into endothelial cells, adipocytes, even smooth muscle cells and skeletal muscle cells using several types of CAL. Afterwards, patients treated with CAL for breast reconstruction post breast cancer showed improvement in subcutaneous tissue thickness and 1 year follow up showed significantly reduced thickness loss in medial breast compared to lipoaspirate without ADSCs enrichment.[52] A case report brought by Tsekouras et al[55] revealed improvement in contour of the post mastectomy breast, up to 22 months follow up using ADSCs in CAL. Furthermore, the amount of cells used in CAL may affect breast volume retention, in which higher number of cells used in enrichment displayed higher volume retention of fat graft compared to using lower number of cells or lower dose of SVF. Subsequently improved long-term volume retention is maintained.[56] The first clinical trial for ADSCs use in breast reconstruction was done and results showed majority of patients feeling satisfied with the result after 1 year. Perez-Cano et al[57] demonstrated the improvement in breast contour deformity with minimal complication the form of cyst due to injection and no cancer recurrence of the breast was reported. Successful restoration of the breast contour has also been reported by Gentile et al,[58] in which CAL proved superior compared to traditional lipotransfer, with 63 % and 39 % volume retention after 1 year, respectively. Interestingly in some cases that has been reported, on top of improvement in reducing volume loss, the area of skin overlying it also showed noticeable rejuvenation.[59]

Implementation of CAL has been attempted at not just post-mastectomy reconstruction, but also breast augmentations. Jung et al revealed that breast augmentation in healthy patients using CAL and SVF had shown a decrease in breast volume by 47 % one-year post procedure. Similarly, Wang et al demonstrated 51 % fat resorption 6 months post CAL breast augmentation of healthy patients.[60] On the contrary, Kamakura et al showed improved breast measurement post CAL breast augmentation that is stable after 9 months follow up, indicating graft viability, whilst with minimal complication in the form of benign cyst.[61] This may demonstrate the complexity in clinical use of SVF and may be due to inadequate numbers of ADSCs in the SVF and skin tension affecting fat absorption.[62]

The ADSCs population with potential of facilitating wound healing and remodelling through formation of fibroblast and generating vascular supply could be a key component in the fat graft long term volume retention. Moreover, ADSCs ability in self renewal, differentiation and in secreting angiogenic factors such as VEGF and HGF as well as modulating local inflammatory response is known to be more robust in hypoxic condition. Immunomodulatory properties of ADSCs were found to be similar with mesenchymal stem cells derived from the bone marrow; they are able to reduce proliferation of mononuclear cells and differentiation of immature dendritic cells.[63] Immunomodulatory cytokine release by ADSCs was explained previously in this review. Recalling the essential role of stem cell niche and the various cell signalling that governs ECSs regulation, certain microenvironment conditions largely affects their survival and function.[64]

Conclusion

The review of literature suggests that cell assisted lipotransfer using adipose-derived stem cells may be a beneficial therapeutic management for breast reconstruction post breast cancer surgical management. The enrichment of autologous ADSCs into grafted fat tissue may result in improved long-term graft retention that supports its clinical advantage. These are due to their inherent properties of multipotent characteristic, angiogenic and immunomodulatory potential. Although a number of studies support this conclusion, some studies also show conflicting result, possibly due to differences in cell isolation methods or number of cells enriched in the graft. Additional studies using a control technique and longer follow up time is encouraged to further investigate the advantages of CAL in maintaining graft survival in breast reconstruction. This is particularly interesting considering the area is prone to microvascular damage and compromised wound healing following radiation therapy.

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Conflict of interest

None.

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